UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,163	11/17/2003	Ricardo Mayo-Alvarez	5009-1	3896

22442 7590 02/07/2006

SHERIDAN ROSS PC
1560 BROADWAY
SUITE 1200
DENVER, CO 80202

EXAMINER	
FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1655	

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/716,163	Applicant(s) MAYO-ALVAREZ ET AL.	
	Examiner Michele Flood	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-24 and 26-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-24 and 26-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on September 23, 2003.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4, 6-24 and 26-40 are under examination.

Response to Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-9, 12-20, 16, 23, 24, 26, 28, 29 and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-9, 16, 23, 24, 26, 28, 29 and 37 are rendered vague and indefinite by the term "from about" because the concurrent use of "from" and "about" fails to adequately describe the dosage range following the recitation of the term. For instance, a composition may comprise "from 'x' mg of a claimed ingredient" or a composition may comprise "about 'x' mg of a claimed ingredient". The lack of clarity renders the claim ambiguous.

Claims 12 and 33 are rendered vague and indefinite by the term "at least about" because the concurrent use of "at least" and "about fails to adequately describe the

dosage range following the recitation of the term. For instance, a composition may comprise "at least 'x' mg of a claimed ingredient" or a composition may comprise "about 'x' mg of a claimed ingredient". The lack of clarity renders the claim ambiguous.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 102

Claims 1 and 10 as amended are rejected under 35 U.S.C. 102(b) as being anticipated by Magruder (A*) and Shaw et al. (B*).

Applicant claims a pharmaceutical composition formulated as a single oral dosage formulation comprising: a. an analgesic selected from the group consisting or morphine meperidine, fentanyl, hydromorphone, oxymorphone, oxycodone, hydrocodone, methadone, pentazocine, levorphenol and combinations thereof: and, b. a stool softener selected from the group consisting of docusate, psyllium, methylcellulose, carboxymethyl cellulose, polycarbophil, and combinations thereof.

Magruder teaches a pharmaceutical composition formulated as a single oral dosage formulation comprising oxycodone (an analgesic) and methylcellulose (a stool softener) in the form of an aqueous suspension, in Column 6, lines 49-60 and in Column 5, line 60 bridging Column 6, line 3.

Shaw teaches a pharmaceutical composition formulated as a single oral dosage formulation comprising methadone (an analgesic) and methylcellulose in the form of a solid, in Column 6, lines 1-15.

The references anticipate the claimed subject matter.

Claims 1, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Shuemaker et al. (C*).

Sheumaker teaches a prolonged release pharmaceutical composition formulated as a single oral dosage formulation comprising an analgesic, *e.g.*, hydrocodone or codeine, and a stool softener, *e.g.*, methylcellulose.

The reference anticipates the claimed subject matter.

Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by LaHann (D*).

Applicant claims a method of preventing constipation during analgesic use comprising administration of a pharmaceutical composition comprising a stool softener selected from the group consisting of docusate, psyllium, methylcellulose, carboxymethyl cellulose, polycarbophil, and combinations thereof with an analgesic in a single oral dosage form, wherein said analgesic is selected from the group consisting of morphine, meperidine, fentanyl, hydromorphone, oxymorphone, oxycodone, hydrocodone, methadone, propoxyphene, pentazocine, levorphanol, and combinations thereof. Applicant further claims the method of claim 21, further comprising a non-opioid analgesic.

LaHann teaches a method of preventing constipation during analgesic use comprising administration of a single oral dosage form comprising proproxyphene (an

analgesic), N-vanillyl-1-E-octadecenamide (a non-opioid analgesic), and methylcellulose (a stool softener) in the form of an oral solution, in Column 8, lines 50-68. *See* entire document, especially Column 1, lines 36-24, Column 6, lines 5-12, as well as, Column 14, line 16 to Column 15, line 44.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 1, 8-12, 16-19, 21, 28-30, 33 and 37-39 as amended remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lazarus et al. (U), as evidenced by the teachings of http:/www.drugs.com/ODR/Senokot Tablets.html (V), Persuad et al. (W), Miller (N) and Herndon et al. (X). The rejection stands for the reasons set forth in the previous office action and for the reasons set forth below.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

Please note that the teachings of Persuad, Miller and Herndon are referred to herein only in response to Applicant's arguments.

In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Applicant's arguments are two-fold. While Applicant reasonably argues that "use of the single dosage form to double the dose of one of the ingredients inherently requires the dosage of the other ingredients present in the dosage form", Applicant does not reasonably argue or provide clear and convincing evidence that the Lazarus' reference teaches away from the instantly claimed formulation and use thereof to provide the claim-designated method of prevention of constipation in a patient receiving analgesia by the administration of an opioid analgesic. For instance, Applicant points out the limitations of the study conducted by the Lazarus team and directs the Office to Figure 1 of the referenced teaching, wherein Lazarus correlates the daily MSC (MS Contin® Tablets; MSC) dosing range (mg) to the mean number of SKS (SENOKOT-S® Tablets; SKS) associated with MSC daily doses (mg). Applicant asserts that since the data taught by Lazarus represents a non-linear increase in the dose amounts of the opioid analgesic to the dose amounts of the laxative used in the method of treatment to prevent opioid-induced constipation in patients receiving pain treatment, one of ordinary skill in the art would not be led to provide the instantly claimed pharmaceutical composition formulated as a single oral formulation because the "currently claimed oral dosage forms cannot be used to separately titrate the analgesic and the laxative." Applicant's arguments have been fully considered but are not fully persuasive for the following reasons. Firstly, despite the obvious limitations to the experimental design of the Lazarus' study and the data obtained thereby, the Office deems that the teachings of Lazarus would still have

been obvious to one of ordinary skill in the art in the making of the instantly claimed inventions, particularly in view of the prior art for the prevention of opioid-induced constipation in patients receiving pain management treatment comprising the administration of an analgesic and a stool softener in a single oral dosage form. For instance, at the time the invention was made, the idea for a method for the prevention or alleviation of constipation in a patient during analgesic treatment by administration of a pharmaceutical composition formulated as single oral dose form comprising an opioid analgesic and a stool softener, and its use thereof was well-known and conventional. For instance, like Applicant's disclosing teachings in the present application, Miller taught a composition as a single oral dosage form comprising an opioid analgesic and a stimulant laxative, namely morphine and bisacodyl. In another instance, Persaud taught a single oral dosage form comprising an opioid analgesic and a stool softener, namely codeine, docusate, paracetamol (acetaminophen) and buclizine hydrochloride. Each of the compositions taught by Miller and Persuad were pharmaceutical compositions in single oral dosage form that was used for the prevention of opioid-constipation in patients. While Applicant argues that it would not be possible to replicate the benefits produced in the Lazarus method of treatment by separately titrating the analgesic and laxative ingredients to provide the instantly claimed pharmaceutical forms, the Office notes that Lazarus expressly teaches, "The study was also designed to assess dosage ratios relating to the use of SENOKOT-S® Tablets, a combination laxative and stool softener containing senna and docusate sodium, for the prevention of opioid-induced constipation", on page 9-12. Lazarus also teaches, "A senna and docusate sodium

preparation (SENOKOT-S® Tablets; SKS) was used to alleviate opioid-induced constipation; consequently there was a significantly lower (p=0.0001) incidence of constipation during treatment with MSC", on page 2, lines 8-12. While Lazarus does teach that dose titration of MSC was allowed to reestablish pain control in individual patients, the data contained therein Figure 1 explicitly details the dose range amounts of the combination laxative and stool softener that is required to prevent constipation in patients receiving a particular dose range amount of morphine. Thus, while the data contained therein Figure 1 does not necessarily equate to a doubling of each of the ingredients to provide the beneficial effect for the prevention of constipation in a patient receiving MSC, the Office notes that the claim-designated method of independent Claim 21 only requires the administration of a stool softener in combination with an analgesic in single oral dosage form without any regard to the amounts of either ingredient, whereas the limitations of dependent Claims 26-29 direct appear to provide a dose range of stool softener to effect the functional effect for the prevention of constipation in a patient (notably "from about 25 mg to about 200 mg of docusate" or "from about 50 mg to about 100 mg of docusate"). The Office further notes that the claim-designated method of treatment of Claim 33 only requires a single oral dosage form comprising an indefinite amount of opioid analgesic to claim-designated amount of docusate, notably "at least about 50 mg of docusate". While the Office cannot determine the scope of a claimed invention by reading limitations into the claims, the Office can look to the specification as a means to define the terms set forth in the claim language and as a means to interpret the scope of the claimed invention, with particular regard to the

method of preparing the instantly claimed pharmaceutical compositions which are useful in the prevention of opioid-induced constipation in a patient. For example, on page 3 of the present specification, line 2 to page 4, line 6, Applicant readily discloses that the claim-designated method of treatment can be achieved by the co-administration of a stool softener with an analgesic in single oral form wherein the pharmaceutical comprises between 10 mg to 300 mg of docusate. On page 6, line 10 to page 7, line 21, Applicant readily discloses that the amount of the opioid analgesic combination used in the making of the claim-designated pharmaceutical form for use in the prevention of constipation in a patient during analgesic use "depends upon the analgesic chosen and whether the dosage form is to be formulated for immediate release or sustained release of the opiate or analgesic combinations." On page 8, line 17 to page 10, line 3, Applicant further discloses that the amount of stool softener used in the making of the instantly claimed pharmaceutical forms is dependent upon the particular type of stool softener used to provide a therapeutic effect in softening the stool of an intended patient receiving opioid analgesic treatment. Applicant further discloses that the experimental parameters to provide the instantly claimed method comprising the use of a single oral dosage formulation of an opioid analgesic and stool softener depends upon the individual chosen opiate, individual chosen opiate, individual chosen stool softener used in the formulation of a single oral dose formulation, and its use thereof wherein the dosing is dependent on a patient's need and perceived perception of pain, time schedule and experimental parameters for the oral administration thereof since stool softeners may effect the absorption rate of the analgesic ingredient contained therein.

Contrary to Applicant's argument that Lazarus teaches away from the instantly claimed inventions, it would appear from Applicant's disclosure that at the time the invention was made it would have been *prima facie* obvious to one of ordinary skill in the art to combine the ingredients taught by Lazarus into a single oral dosage form for use in the claim-designated method of treatments since the data contained therein Figure 1 of the Lazarus' reference explicitly details the dose range amounts of the combination laxative and stool softener that is required to prevent constipation in patients receiving a particular dose range amount of morphine, and since the Lazarus' study details the same experimental parameters for determining the beneficial functional effect for prevention of constipation receiving MSC by co-administration of an effective amount of an a stool-softener in combination with a laxative, and since the prior art teachings of Miller and Persuad taught the combination of an analgesic in combination with a stool softener or laxative could reduce unwanted side-effects of opioid-induced constipation. For instance, even Miller teaches that the amount of the laxatives employed in the making of a single oral dose formulation comprising an opioid analgesic in combination with a laxative depends upon the nature of the particular laxative. *See* page 2 to page 3. In another instance, Herndon also teaches that prophylaxis of opioid-induced constipation can be effected by the oral administration of stool softeners, such as docusate, or bulk-forming laxatives, such as psyllium, or peristalsis-increasing agents or stimulant laxatives, such as senna and bisacodyl. *See* page 244 to page 247, under "*Pathophysiology of Opioid-Induced Constipation*".

Thus, with Lazarus teaching a method of alleviating opioid-induced constipation comprising orally administering controlled-release morphine sulfate and 60-180 mg of Senokot-S® (a combination laxative and stool softener containing senna and 50 mg of docusate, as evidenced by the teachings of drugs.com) except for wherein the pharmaceutical composition comprises the analgesic and the stool softener in a single dosage form, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the instantly claimed old and well-known ingredients taught by Lazarus to provide the instantly claimed inventions because Lazarus teaches that the simultaneous administration of morphine and docusate reduces the frequency of constipation in patients receiving pain control treatment by the administration of an opioid analgesic, on page 12, line 38 and page 13 in its entirety. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the form of the pharmaceutical composition and the method of oral administration of the two ingredients taught by Lazarus to provide the instantly claimed inventions because it would have been merely a matter of judicious selection to pick and choose the dosage form of the ingredients comprising the pharmaceutical composition given that the reference before him or her clearly teaches that the ingredients when simultaneously and orally administered provide the claim-designated functional effect for the prevention of constipation in humans receiving opioid analgesic treatment, especially since a single dose form would provide a convenient and easy dosage form for administration to patients in need of such therapeutic treatment; and, since Lazarus teaches, "Controlled-

release oral morphine sulfate (MS Contin® Tablets*; MSC), represents an innovation over conventional immediate-release morphine and over the longer-acting narcotics because of its convenient 12-hour dosing schedule and ease of administration combined with an efficacy and safety profile at least equal to that seen with conventional oral morphine", on page 3, lines 13-21; and, given the references of Persaud, Miller and Herndon.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-4, 8-24, 28-40 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lazarus et al. (U), as evidenced by the teachings of http:/www.drugs.com/ODR/Senokot Tablets.html (V) in view of Kaiko et al. (E*). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth immediately above.

A method of preventing constipation during analgesic use comprising administration of a single solid dosage form comprising an opioid analgesic and at least about 50 mg of docusate is set forth immediately above, as obviated by the teachings of Lazarus . The obvious teachings of Lazarus teaches the instantly claimed invention except for wherein the single dose and the method for the oral administration thereof prevents constipation comprises the non-opioid analgesic acetaminophen; and wherein the opioid analgesic is codeine. However, it would have been obvious to one of

ordinary skill in the art to modify the teachings of Lazarus by adding the instantly claimed acetaminophen to the method and the composition taught by Lazarus and to replace and/or add the opioid analgesic codeine to the composition taught by the obvious teachings of Lazarus because at the time the invention was made the addition of acetaminophen to a composition used in the treatment of patients receiving opioid analgesic treatment was known for its beneficial effect, as evidenced by the teachings of Kaiko; and, Lazarus taught a conversion factor to determine the daily dose of opioids other than morphine or a combination thereof (*e.g.,* hydromorphone, methadone, levorphanol, oxymorphone, meperidine, oxycodone, codeine and pentazocine, *etc.*). Firstly, Kaiko teaches a pharmaceutical composition in solid dose form comprising an analgesic opioid, *e.g.,* codeine and hydrocodone, and acetaminophen (non-opioid analgesic) in a sustained release form for release of the ingredients over a period of time. In Column 11, line 49 to Column 12, line 3, Kaiko teaches that codeine, morphine, meperidine, fentanyl, hydromorphone, oxymorphone, oxycodone, hydrocodone, methadone, propoxyphene, pentazocine, levorphanol, and combinations thereof may be used in the making of his compositions. In Column 14, lines 27-49, Kaiko teaches that the amount of acetaminophen comprising the referenced composition is an amount of about 10 mg to about 2000 mg; and, in an amount of about 325 mg to about 1000 mg. In Column 34, lines 24-39, Kaiko further teaches orally administering hydrocodone and acetaminophen to patients under fasted conditions. Secondly, Lazarus teaches that a conversion factor can be conveniently used to determine the daily dose equivalent of one opioid for the equivalent dose of MSC. At the time the invention was made, one of

ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the acetaminophen taught by Kaiko, and to substitute and/or add the MSC taught by Lazarus for codeine or any other equivalent opioid analgesic to provide the instantly claimed inventions because Kaiko teaches that it was old and well-known in the art at the time the invention was made that acetaminophen can act synergistically with opioids and that such compositions comprising acetaminophen are also said to be subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression, in Column 14, lines 50-58; furthermore, in Column 34, lines 24-39, Kaiko teaches oral administrations of the reference compositions to provide the beneficial functional of this compositions to human subjects are effective under fasted conditions; and, Lazarus teaches that the simultaneous oral administration of morphine and docusate provides a method for the amelioration of constipation during analgesic use and that other opioid analgesics, such as the instantly claimed codeine is a functional equivalent of the referenced codeine (MSC). Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,*

47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, the instantly claimed inventions are no more than the combining of well-known ingredients and well-known methods for reducing the risk of or preventing adverse pharmacological side effects, such as constipation and drug addiction, in human subjects receiving analgesic therapy by the oral administration of opioids.

As each of the references indicate that the various proportions and amounts of the ingredients used in the claimed composition or the claimed composition/pharmaceutical combinations, as well, as the method steps for the administration thereof are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Claims 1-4, 8-24 and 28-40 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lazarus et al. (U), as evidenced by the teachings of http:/www.drugs.com/ODR/Senokot Tablets.html (V), and Kaiko et al. (E*) in view of Colliopoulos (G*) and Kais et al. (F*). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth above.

The combined teachings of Lazarus and Kaiko are set forth above. The combined teachings of Lazarus and Kaiko teach the instantly claimed inventions except for wherein the stool softener is psyllium. However, it would have been obvious to one

of ordinary skill in the art to add psyllium to the composition and method of use thereof taught by the combined teachings of Lazarus and Kaiko to provide the instantly claimed inventions because at the time the invention was made psyllium and docusate were known in the art for their beneficial functional effect, as evidenced by the teachings of Colliopoulos and Kais. Firstly, Colliopoulos teaches a dietary food composition comprising dioctyl sulfosuccinate (docusate) and psyllium having a laxative effect. Secondly, Kais teaches a composition comprising encapsulated dioctyl sulfosuccinate (docusate) and psyllium having a laxative effect. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add and/or replace the stool softener used in the method of making the pharmaceutical composition and method of use thereof taught by the combined teachings of Lazarus and Kaiko to provide the instantly claimed pharmaceutical compositions and method of treatments because Colliopoulos teaches that the reference pharmaceutical compositions comprising psyllium may be dispersed in a palatable food product and orally administered to human subjects to provide a method of constipation; and, Kais teaches that the reference pharmaceutical compositions comprising docusate and psyllium may be used in the making of food products and orally administered to human subjects to provide a method of treating constipation. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed composition because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for

the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, the instantly claimed inventions are no more than the combining of well-known ingredients and well-known methods for reducing the risk of or preventing adverse pharmacological side effects, such as constipation and drug addiction, in human subjects receiving analgesic therapy by the oral administration of opioids.

As each of the references indicate that the various proportions and amounts of the ingredients used in the claimed composition or the claimed composition/pharmaceutical combinations, as well, as the method steps for the administration thereof are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

No claims are allowed.

* Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Should you receive inquiries about the use of the Office's PAIR system, applicants may be referred to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele C. Flood

MICHELE FLOOD
PRIMARY EXAMINER

Michele Flood
Primary Examiner
Art Unit 1655

MCF
January 9, 2006